Annex to: Update of the risk assessment on tetrabromobisphenol A (TBBPA) and its derivatives in food. doi:10.2903/j.efsa.2024.8859

ANNEX D – Protocol and Results of Expert Knowledge Elicitation

This Annex describes the Expert Knowledge Elicitation (EKE) protocol and results for the uncertainty analysis for the update of the opinion on tetrabromobisphenol A (TBBPA) and its derivatives in food.

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1. Context

Subject	Description
Context	Update of the Scientific Opinion on tetrabromobisphenol A (TBBPA) and its derivatives in food
Problem	Uncertainty analysis
Path to a solution (risk assessment model)	Identification and prioritisation of uncertainties Quantification of their combined impact on the main conclusion(s)
Parameters for EKE	EKE on overall uncertainty for risk characterisation
Mandate/question	EFSA-Q-2018-00434
Panel	CONTAM
Working group	CONTAM WG on BFRs
Responsible EFSA unit/team	Luisa Ramos Bordajandi
Intended output	Final uncertainty assessment

EKE: Expert Knowledge Elicitation; EFSA: European Food Safety Authority; CONTAM: Contaminants in the Food Chain; WG: working group; BFR: brominated flame retardant.

1.1. Terms of Reference relevant for this evidence dossier

See **Sections 1.1** and **1.2** of the Opinion. In accordance with Art. 29 (1) of Regulation (EC) No 178/2002,[1] the European Commission asks the European Food Safety Authority (EFSA) for an updated exposure assessment for the brominated flame retardants (BFRs), covered by Recommendation 2014/118/EU,[2] taking into account the occurrence data in food, submitted after the publication of the 2010–2012 EFSA scientific Opinions, and an updated consumer risk assessment, taking into account newly available scientific information.

1.2. Elicitation group

The EKE followed a semiformal approach and was performed within the working group (WG) BFRs. Experts for the elicitations (elicitation groups) were subgroups of the WG, as follows.

Risk characterisation EKE

Role	Name
EKE experts	Diane Benford
	Laurent Bodin
	Christer Hogstrand
	Evangelia Ntzani
	Francesca Riolo
	Martin Rose
	Henri Schroeder
	Christiane Vleminckx
EKE facilitator	Andy Hart
Rapporteurs	Eirini Kouloura and Luisa Ramos Bordajandi

EKE: Expert Knowledge Elicitation.

1.3. Timeline

The different steps were performed according to the development of the draft Opinion.

[1] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–24.

[2] Commission Recommendation of 3 March 2014 on the monitoring of traces of brominated flame retardants in food (text with EEA relevance) (2014/118/EU). OJ L 65, 5.3.2014, p. 39–40.

The EKE protocol followed a draft standard procedure for the uncertainty assessment of the Panel on Contaminants in the Food Chain (CONTAM Panel). Necessary adaptations were made for each elicitation.

Date	Topic
Elicitation group (pre-elicitation)	
From March 2023 onwards	Preparation of the draft Opinion (i.e. evidence dossier)
From June 2023 onwards	Development of the uncertainty analysis
From November 2023 onwards	Framing of the EKE question(s)
Elicitation group (elicitation sessions)	
9 January 2024	Training of the experts
15 February 2024	Elicitation session Risk Characterisation
February 2024	Technical report on the elicitation (this document)
February 2024	Result report (draft Opinion sections on uncertainty analysis)
March 2024	Review of the result report
March 2024	Feedback to the experts
Finalisation	
March 2024	Final technical and result reports

EKE: Expert Knowledge Elicitation.

2. Evidence dossier

All evidence used in the assessment and EKE was documented in the draft Opinion.

2.1. Description and prioritisation of identified uncertainties

The experts identified, described and prioritised sources of uncertainty affecting the exposure, hazard and risk assessments using the tables in the CONTAM Panel's tool for uncertainty identification (see **Appendix I**).

3. Elicitations

3.1. Assessment of overall uncertainty for risk characterisation

3.1.1. Elicitation group

See **Section 1.2** of this **Annex D**. In total, 7 experts participated in the first round of judgements and 8 experts in the second round and consensus discussion.

3.3.2. EKE question and definitions

Question: What is your % probability that, if all of the identified non-standard uncertainties affecting the assessment were resolved (e.g. by obtaining more or better data), current dietary exposure to TBBPA would not raise a health concern for any type of health effect for any of the population groups and surveys considered at either the mean or 95th percentile (P95) of chronic exposure?

Definitions:

- All of the identified non-standard uncertainties affecting the assessment: see **Appendix I** (Tables I.1, I.2 and I.3).
- The population groups and surveys considered: the age groups considered for the total population (infants, toddlers, etc.) and the specific groups of formula-fed infants and breastfed infants, as documented in **Section 3.3.1** of the Opinion.

3.3.3. EKE training

All of the experts had received training and participated in EKEs for previous EFSA assessment(s). As a reminder, the facilitator gave a short presentation on:

- the use and meaning of subjective probability for quantifying uncertainty;
- the evidence and reasoning to consider when making judgements for this EKE;
- the need to guard against natural psychological biases affecting expert judgement.

3.3.4. Elicitation procedure

- The wording of the EKE question was discussed and agreed upon by the WG members.
- Seven of the experts participated in the first round of judgements. The facilitator sent them an email (copied to all members of the WG) with a document containing the EKE question and a template for providing their judgement and reasoning, a copy of the slides used in the training (**Section 3.3.3** above), and comparisons of the exposure estimates with the tolerable daily intake (TDI) and some alternative scenarios for hazard characterisation.
- The facilitator anonymised and collated the first judgements and reasoning provided by the experts into a single document, which was sent to the experts.
- At the meeting on 15 February 2024, the judgements and reasoning of each expert in turn were displayed on screen, and the expert was asked to summarise and discuss them. One additional expert, who had been unable to contribute earlier due to other commitments, joined the process at this stage and participated in the discussion and in the second round of judgements.
- After each expert had spoken, the WG agreed upon some clarifications to the original wording of the EKE question (adding the word 'dietary' and confirming that the list of population groups was to be included, as shown in **Section 3.3.2** above). Then, the facilitator displayed and explained a summary of the updated calculations comparing hazard and exposure.
- The meeting was paused, and the experts were asked to review their first judgements and reasoning, revise them in the light of the discussion if they wished to, and send them to the facilitator before the meeting continued on the same day.
- The facilitator anonymised and collated the second (final) judgements and displayed them on the screen.
- The facilitator then led a discussion with all experts involved to seek a consensus judgement on the EKE question, after first explaining the type of consensus sought in the Sheffield method for EKE (EFSA, 2014).
- The second (final) judgements and reasoning provided by the experts were added into the document with the first judgements and sent to the experts. This together with the rapporteur's notes of the discussions were used by the WG to prepare a summary of the reasoning for the consensus judgement, to be included in the Opinion.

3.3.5. Elicitation results

3.3.5.1. Individual judgements

The first and second (final) judgements of the hazard experts are summarised below.

Expert	**Question: What is your % probability that, if all of the identified non-standard uncertainties affecting the assessment were resolved (e.g. by obtaining more or better data), current dietary exposure to TBBPA would not raise a health concern for any type of health effect for any of the population groups and surveys considered at either the mean or P95 of chronic exposure?**	
	First judgement (%)	**Second judgement (%)**

A	95	90–95
B	90–95	90–95
C	90	90
D	80	90
E	95–99	–
F	90–95	90–95
G	90	90–95
H	–	80

–: Expert could not participate to the round of judgements.

3.3.5.2. Consensus judgement

After discussing and refining their individual judgements and reasoning, the experts worked towards a consensus conclusion. In summary, the following considerations were discussed:

- The highest TBBPA exposure estimate (for formula-fed infants at the P95 of both consumption and occurrence) was a factor of 2.6 below the TDI based on the lowest-observed-adverse-effect level (LOAEL) of 0.2 mg/kg body weight (bw) per day for decreased interest in social interaction in mice. This is slightly less than the additional factor of 3 recommended by the EFSA Scientific Committee (2017) to allow for increased inter-individual toxicokinetic variability when considering infants below 16 weeks of age. However, this was an upper bound (UB) estimate of exposure, and the true exposure is likely to be much closer to the lower bound (LB), which was a factor of 14 below the TDI (see **Section 2.3.2** of the Opinion). Exposure estimates for all other population groups were at least a factor of 5 below the TDI, making it almost certain that current dietary exposure to TBBPA does not raise a health concern.
- TBBPA was concluded to be carcinogenic but almost certainly (≥99% probability) via non-genotoxic mechanisms (see **Section 3.5.2**). The lowest acceptable $BMDL_{10}$ for a cancer end point (41.6 mg/kg bw per day for uterine atypical endometrial hyperplasia from NTP, 2014) was 2 orders of magnitude above the LOAEL of 0.2 mg/kg bw per day for decreased interest in social interaction. Even if TBBPA was directly genotoxic, the lowest margin of exposure would be over 300,000 and, therefore, considered to be of low concern.
- There was a LOAEL of 0.1 mg/kg bw per day identified for increased level of activity in the running wheel apparatus (first experiment in Rock et al., 2019), which is a factor of 2 closer to the dietary exposure estimates than the LOAEL of 0.2 mg/kg bw per day for decreased interest in social interaction (Kim et al., 2015), which is the Reference Point for the establishment of the TDI. However, the relevance for humans and adversity of an increased activity level in the running wheel apparatus was uncertain. This, together with the other uncertainties affecting this end point and the exposure estimates, made it extremely unlikely that this effect would raise a health concern.
- Effects on thyroid, reproduction and neurotoxicity end points were reported at exceptionally low levels in a series of studies where mice were exposed to TBBPA via drinking water (Zatecka et al., 2014; Li et al., 2022; Xiong et al., 2023; Song et al., 2024). These studies were generally well conducted, but the concentrations in the drinking water were not confirmed by analysis of TBBPA, which may be important, e.g. because of the low solubility of TBBPA in water. Thus, there is a high level of uncertainty regarding the doses received by the animals. If resolving this uncertainty would confirm the occurrence of effects at the lowest level reported in these studies (5 µg/kg bw per day), it could result in a lower tolerable intake, which would be exceeded by the UB estimates of exposure for infants in the general population and formula-fed infants and also by the highest estimates of exposure for breastfed infants (which were medium bound (MB) but based on 'total TBBPA' rather than 'free TBBPA'). Taking account of the high uncertainty regarding the calculation of the dose levels in these toxicity studies and the uncertainties affecting the different exposure

estimates, the experts considered it possible but very unlikely that these effects raise a health concern.

Based on these considerations, the experts agreed on a consensus judgement of 90–95% probability that current dietary exposure to TBBPA would not raise a health concern for any of the surveys and population groups considered, including breastfed and formula-fed infants.

A lower probability of 80% was given by 1 expert, noting the increasing evidence of the sensitivity of the developing brain to chemical exposure, including mode of action (MOA) studies with TBBPA reported in the Opinion. These indicate some probability that relevant effects of TBBPA may be found at lower dose levels in future, though these might be intermediate rather than apical.

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Abbreviations

EKE	Expert Knowledge Elicitation
TBBPA	tetrabromobisphenol A
WG	working group
PBDE	polybrominated diphenyl ether
CONTAM Panel	EFSA Panel on Contaminants in the Food Chain
P95	95th percentile
TDI	tolerable daily intake

LOAEL	lowest-observed-adverse-effect level
UB	upper bound
LB	lower bound
MB	medium bound
MOA	mode of action